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Multi-component synthesis of piperidines and dihydropyrrol-2-one derivatives catalyzed by a dual-functional ionic liquid

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Narjes Basirat, Seyed Sajad Sajadikhah and Abdolkarim Zare

Abstract

N,N,N',N'-tetramethyl-*N,N'*-bis(sulfo)ethane-1,2-diaminium mesylate ([TMBSED][OMs]$_2$) was employed for the synthesis of piperidines and dihydropyrrol-2-ones *via* one-pot multi-component reactions in simple and green processes. This pseudo five-component reaction of aromatic aldehydes, anilines and alkyl acetoacetates was carried out under reflux conditions in ethanol to afford substituted piperidines. Also, dihydropyrrol-2-one derivatives were synthesized by means of four-component reactions of various amines, dialkyl acetylenedicarboxylates and formaldehyde in ethanol at room temperature. The present approaches have several advantages such as good yields, easy work-ups, short reaction times, and utilize mild and clean reaction conditions.

Keywords

ionic liquid, [TMBSED][OMs]$_2$, piperidine, dihydropyrrol-2-ones, multi-component reactions

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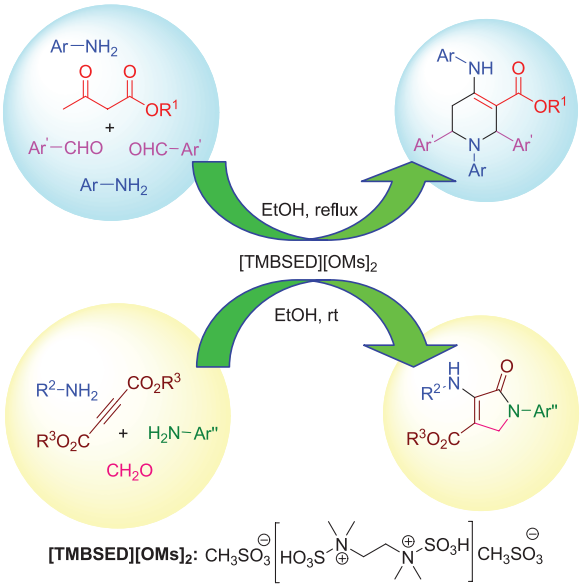


Introduction

In recent years, ionic liquids (ILs) have been extensively used and have attracted remarkable research interest as catalysts for the green synthesis of the organic compounds due to their tunable physical and chemical properties.[1] ILs have also been employed because of their advantages, including high thermal and chemical stability, low vapor pressure, non-flammability, and good ionic conductivity, as well as ability to catalyze numerous types of organic reactions, their ability to be used in solvent-free or solution

Department of Chemistry, Payame Noor University (PNU), Tehran, Iran

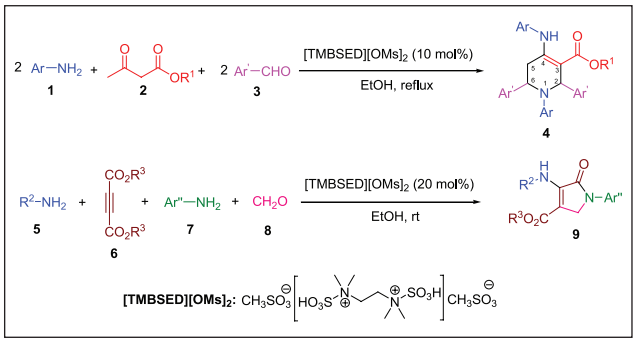
Corresponding author:
Seyed Sajad Sajadikhah, Department of Chemistry, Payame Noor University (PNU), P.O. Box 19395-3697, Tehran, Iran.
Email: sssajadi@pnu.ac.ir

conditions, the ease of changing the cation or anion in their structures to modify their physical and chemical properties, and their ability to dissolve in many organic and inorganic materials.[2–5]

Piperidine derivatives, as a valuable class of nitrogen-containing heterocycles, have received much attention owing to their properties such as anti-hypertensive,[6] neurotoxic activity,[7] anti-bacterial,[8] treatment of Alzheimer's diseases,[9] anticonvulsant, anti-inflammatory,[10] anticancer,[11] and antimalarial.[12] Recently, multicomponent reactions (MCRs) have been employed for the synthesis of substituted piperidines.[13–22]

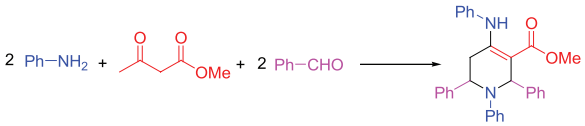
In addition, dihydropyrrol-2-ones are important in organic synthesis due to their wide spectrum of activity which includes anti-microbiological,[23,24] antitumor,[25,26] anti-inflammatory,[27] antimalarial,[28] antifungal,[29] antidiabetics,[30] and antibiotic properties.[31] Therefore, many methodologies have been developed to synthesize these practical heterocycles.[32–38] However, some of the above-mentioned methods for the synthesis of both those types heterocycles have disadvantages such as long reaction times, low or moderate yields, and environmental pollution. Hence, the development of beneficial and environmentally friendly methods for the preparation of these compounds is still in demand.

In this work, *N,N,N',N'*-tetramethyl-*N, N'*-bis(sulfo) ethane-1,2-diaminium mesylate ([TMBSED][OMs]$_2$) was used as an effective dual-functional IL for the synthesis of substituted piperidines and dihydropyrrol-2-one derivatives *via* one-pot MCRs in ethanol as a green solvent (Scheme 1).



Scheme 1. Synthesis of piperidines **4** and dihydropyrrol-2-ones **9** in the presence of ([TMBSED][OMs]$_2$).

Table 1. Optimization of the reaction conditions for the synthesis of **4a**.



Entry	Catalyst (mol%)	Temp (°C)	Time (min)	Yield (%)[a]
1	5	rt	100	—
2	10	rt	100	25
3	15	rt	100	32
4	5	50	80	59
5	10	50	75	62
6	15	50	65	62
7	5	reflux	60	80
8	10	reflux	55	93
9	15	reflux	55	94

[a]Isolated yield.

Results and discussions

[TMBSED][OMs]$_2$ was synthesized according to the our previously reported work.[39] To optimize the amount of the catalyst for the synthesis of substituted piperidines, the reaction of aniline (2 mmol), methyl acetoacetate (1 mmol), and benzaldehyde (2 mmol) was selected as a model system. Next, 5, 10, and 15 mol% of [TMBSED][OMs]$_2$ were examined at ambient temperature, 50°C, and reflux conditions in EtOH. According to the results in Table 1, 10 mol% of the IL catalyst afforded methyl 1,2,5,6-tetrahydro-1,2,6-triphenyl-4-(phenylamino)pyridine-3-carboxylate (**4a**) in 93% yield under reflux conditions in 55 min as the best result (Table 1, entry 8).

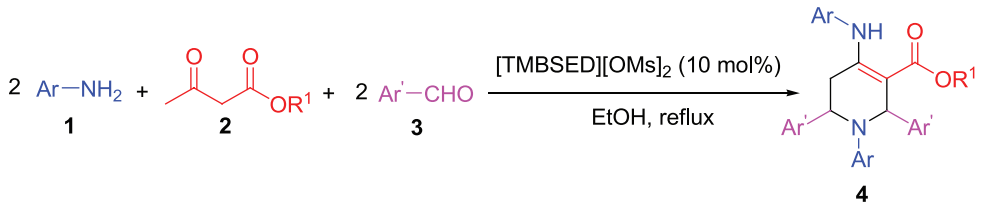
Next, the pseudo five-component reaction of anilines **1** (2 mmol), methyl/ethyl acetoacetate **2** (1 mmol) and aromatic aldehydes **3** (2 mmol) was investigated under the optimized conditions for the preparation of functionalized piperidines **4a-j** (Table 2). A wide range of substituted and structurally diverse aldehydes and anilines was utilized to give the corresponding products in high to excellent yields using the acidic IL. Next, we examined *n*-heptanal and *n*-heptylamine as examples of aliphatic aldehydes and amines instead of benzaldehyde and aniline, respectively. However, the desired products were not obtained (Table 2, entries 11 and 12). This may be due to the tendency of aliphatic aldehydes to produce enamines rather than imines and that these condense with any remaining aldehyde. In addition, in the presence of n-heptylamine, the higher basicity of the aliphatic amine compared to aniline can lead to salt formation with the catalyst.[40]

Based on the literature,[14–16] the proposed mechanism for this pseudo five-component reaction is displayed in Scheme 2. It was assumed that the aniline **1** reacts with the *β*-ketoester **2** to give enamine **A** in the presence of [TMBSED][OMs]$_2$ and that it also reacts with aldehyde **3** to give imine **B** with elimination of water. Afterwards, the reaction of enamine **A** and activated imine **B** *via* an intermolecular Mannich-type reaction led to intermediate **C**. The reaction of intermediate **C** with a second molecule of the aldehyde produces intermediate **D**, which undergoes tautomerization to afford intermediate **D**. Following an intramolecular Mannich-type reaction to form intermediate **E**, deprotonation and tautomerization provided the corresponding functionalized piperidine **4**.

To demonstrate the applicability of the presented work, it can be compared with several reported results in the literature. The results show that the reactions were performed in short times and gave excellent yields in the presence of [TMBSED][OMs]$_2$ when compared to other catalysts (Table 3).

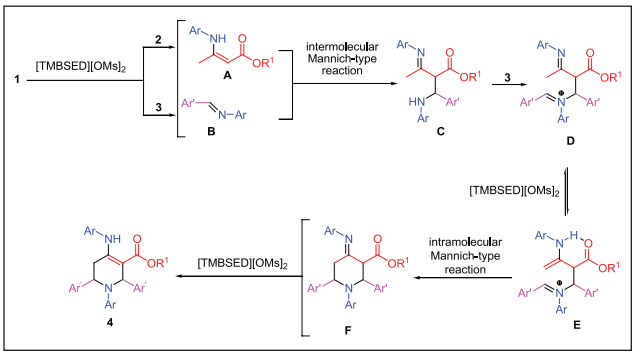
We next synthesized dihydropyrrol-2-ones **9** using the [TMBSED][OMs]$_2$ catalyst. First, optimization studies were performed using aniline (2 mmol), dimethyl

Table 2. Preparation of functionalized piperidines **4a-j** in the presence of $[TMBSED][OMs]_2$.



Entry	Ar	Ar'	R^1	Product	Time (min)	Yield (%)[a]	M.p. (°C)	
							Found	Reported
1	Ph	Ph	Me	**4a**	55	93	180–182	185–186[15]
2	Ph	4-MeO-C_6H_4	Me	**4b**	60	94	188–189	186–188[15]
3	Ph	4-Me-C_6H_4	Et	**4c**	60	87	224–226	228–231[15]
4	4-MeO-C_6H_4	4-Me-C_6H_4	Et	**4d**	60	81	219–221	221–224[16]
5	4-Me-C_6H_4	4-Me-C_6H_4	Et	**4e**	70	95	169–171	169–171[22]
6	4-Me-C_6H_4	Ph	Me	**4f**	55	88	194–196	190–192[20]
7	4-Cl-C_6H_4	4-Br-C_6H_4	Me	**4g**	60	88	161–162	160–163[12]
8	4-Br-C_6H_4	Ph	Et	**4h**	60	90	196–198	196–198[22]
9	4-Cl-C_6H_4	Ph	Me	**4i**	55	89	205–207	202–203[12]
10	Ph	4-O_2N-C_6H_4	Me	**4j**	120	52	234–236	239–242[12]
11	*n*-heptylamine	Ph	Et	—	24 h	—	—	—
12	Ph	*n*-heptanal	Et	—	24 h	—	—	—

[a]Isolated yield.



Scheme 2. The proposed mechanism for the preparation of piperidine derivatives.

acetylenedicarboxylate (1 mmol) and formaldehyde (1.5 mmol) in EtOH as a model reaction. The reaction was carried out with 10, 20, and 30 mol% of the catalyst at room temperature over 2.5–3 h and the corresponding product **9a** was obtained in yields of 80%, 95%, and 96%. Increasing the amount of catalyst to 30 mol% did not increase the reaction yield further. Therefore, the substrate scope of the reaction was investigated utilizing a range of structurally diverse aliphatic and aromatic amines and dimethyl/ethyl acetylenedicarboxylates in the presence of 20 mol% of $[TMBSED][OMs]_2$. The corresponding dihydropyrrol-2-ones **9a-j** were synthesized in good to high yields in short reactions times (Table 4).

A possible reaction mechanism for the preparation of dihydropyrrol-2-ones **9** is presented in Scheme 3.[34] First, the reaction of amine **5** with dialkyl acetylenedicarboxylate **6** leads to intermediate **G**. Second, condensation between amine **7** and formaldehyde **8** in the presence of $[TMBSED][OMs]_2$ produces imine **H**. Reaction between intermediate **G** and imine **H** then generates intermediate **I**. Cyclization of intermediate **I** leads to intermediate **J**, which in the final step tautomerizes to give the corresponding dihydropyrrol-2-one **9**.

A comparison the results obtained with $[TMBSED][OMs]_2$ and some reported catalysts for the synthesis of product **9c** shows that $[TMBSED][OMs]_2$ can act as effective and efficient catalyst with respect to the reaction time and yield (Table 5).

Conclusion

In summary, we have developed efficient one-pot procedures for the synthesis of functionalized piperidines and dihydropyrrol-2-one derivatives using $[TMBSED][OMs]_2$ as a catalyst. These methods offered several advantages such as short reaction times, good to high yields, simplicity in operation, no need for column chromatography, and a green aspect by using ethanol as the solvent.

Experimental

Materials

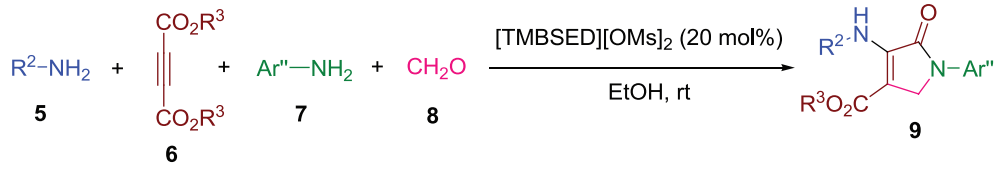
All chemicals were obtained from Merck, Fluka and Sigma-Aldrich and were used without subsequent purification. The nuclear magnetic resonance (NMR) spectra were recorded with a Bruker DRX-400 AVANCE instrument (400 MHz for ^1H, 100 MHz for ^{13}C) in dimethyl sulfoxide (DMSO)-d_6 as solvent. Melting points were measured on an Electro thermal 9100 apparatus. Please see the supplemental material for the spectral data of some selected compounds.

Table 3. Comparison the results of [TMBSED][OMs]$_2$ with other catalysts in the synthesis of compound **4a**.

Entry	Catalyst (mol%)	Conditions	Time	Yield (%)[a] [Ref]
1	Iodine (10 mol%)	MeOH, rt	8 h	81[15]
2	$ZrOCl_2.8H_2O$ (20 mol%)	EtOH, reflux	3.5 h	80[13]
3	TBATB (10 mol%)	EtOH, rt	24 h	74[14]
4	[Hpyro][HSO_4] (15 mol%)	EtOH, reflux	8 h	77[21]
5	$Al(H_2PO_4)_3$ (0.1 g)	EtOH, rt	12 h	80[20]
6	CAN (15 mol%)	MeCN, rt	20 h	82[16]
7	[TMBSED][OMs]$_2$ (10 mol%)	EtOH, reflux	55 min	93 (present work)

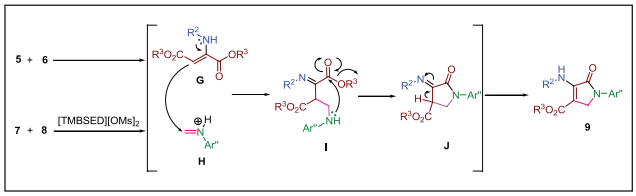
[a]Yields refer to isolated pure products based on the reaction of aniline (2 mmol), methyl acetoacetate (1 mmol) and benzaldehyde (2 mmol).

Table 4. Preparation of dihydropyrrol-2-one derivatives in the presence of [TMBSED][OMs]$_2$.



Entry	R^2	R^3	Ar″	Product	Time (h)	Yield (%)[a]	M.p. (°C)	
							Found	Reported
1	Ph	Me	Ph	**9a**	2.5	95	152–154	155–156[34]
2	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**9b**	2	93	171–173	173–174[34]
3	4-Me-C_6H_4	Me	4-Me-C_6H_4	**9c**	2.5	91	175–177	177–178[34]
4	Ph	Et	Ph	**9d**	3	90	134–136	138–140[33]
5	4-MeO-C_6H_4	Et	4-MeO-C_6H_4	**9e**	3	85	152–154	152–154[20]
6	*n*-C_3H_7	Et	Ph	**9f**	2.5	89	76–77	78–79[33]
7	*n*-C_4H_9	Me	4-Cl-C_6H_4	**9g**	2.5	90	92–94	92–94[38]
8	*n*-C_4H_9	Et	4-Br-C_6H_4	**9h**	2.5	92	94–96	94–96[35]
9	Ph-CH_2	Me	4-Me-C_6H_4	**9i**	2	94	143–145	144–146[38]
10	Ph-CH_2	Me	Ph	**9j**	2	90	137–138	139–140[34]

[a]Isolated yield.



Scheme 3. The proposed mechanism for the synthesis of dihydropyrrol-2-ones 9.

Table 5. Comparison the results of [TMBSED][OMs]$_2$ with other catalysts in the synthesis of compound **9c**.

Entry	Catalyst	Conditions	Time (h)	Yield (%)[a] [Ref]
1	Iodine (10 mol%)	MeOH, rt	1	78[34]
2	Nano-$TiCl_4$/SiO_2(0.08 g)	EtOH, 70°C	2.5	80[32]
3	*p*-TsOH·H_2O (15 mol%)	MeOH, rt	3	83[38]
4	$Cu(OAc)_2·H_2O$ (80 mg)	MeOH, rt	6	91[37]
5	[TMBSED][OMs]$_2$ (20 mol%)	EtOH, rt	2.5	91 (present work)

[a]Yields refer to isolated pure products.

General procedure for the synthesis of piperidines 4

A solution of aromatic amine **1** (2 mmol) and alkyl acetoacetate **2** (1 mmol) in ethanol (10 mL) was stirred for 30 min in the presence of [TMBSED][OMs]$_2$ (10 mol%) at room temperature. Next, the aromatic aldehyde **3** (2 mmol) was added and the reaction mixture was allowed to stir for the appropriate amount of time under reflux. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature. The resulting precipitate was collected by filtration and washed with EtOH (3 × 2 mL) to give the pure product.

General procedure for the preparation of dihydropyrrol-2-ones 9

A mixture of amine **5** (1 mmol) and dialkyl acetylenedicarboxylate **6** (1 mmol) in EtOH (10 mL) was stirred for 30 min. Next, amine **7** (1 mmol), formaldehyde **8** (1.5 mmol) and [TMBSED][OMs]$_2$ (20 mol%) were added successively. The reaction mixture was allowed to stir at room temperature for the appropriate amount of time. After completion of the reaction (monitored by TLC), the solid precipitate was

filtered off and washed with EtOH (3 × 2 mL) to give the pure product **9**.

Declaration of conflicting interests

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ORCID iD

Seyed Sajad Sajadikhah https://orcid.org/0000-0002-4415-5325

Supplemental material

Supplemental material for this article is available online.

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